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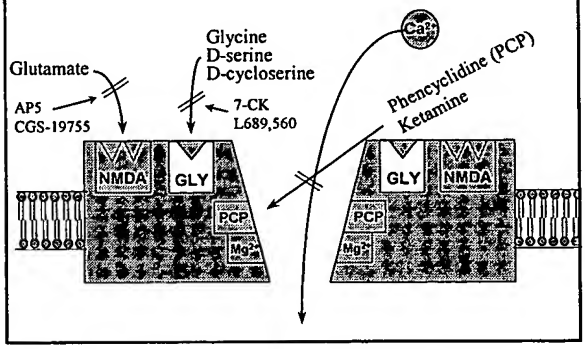
D-serine transport antagonists for treatment of schizophrenia

Inventor: Daniel C. Javitt

NMDA RECEPTOR COMPLEX

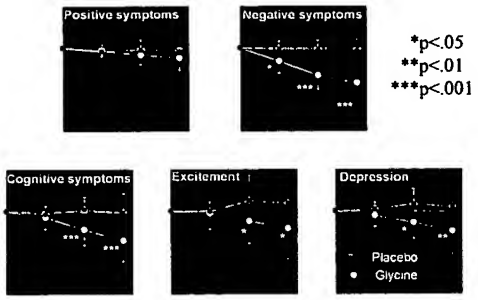


Positive and Negative Symptom Scale (PANSS) – 5 factor model

Positive	Negative
Delusions	Emotional withdrawal
Unusual thought content	Passive/apathetic withdrawal
Grandiosity	Lack of spontaneity
Suspiciousness/persecution	Poor rapport
	Blunted affect
	Active social avoidance

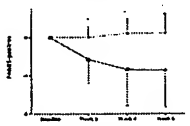
Cognitive	Excitement	Depression
Conceptual disorganization	Excitement	Anxiety
Disorientation	Poor impulse control	Guilt feelings
Difficulty in abstract thinking	Hostility	Depression
Mannerisms and posturing	Tension	Somatic concern
Poor attention		Preoccupation

Glycine treatment (60 g/d) + typical antipsychotic

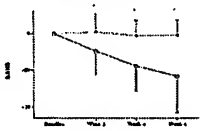


D-Serine 0.03 g/kg/day (2.1 g/day) - Taiwan

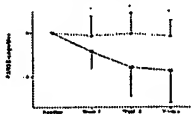
Positive



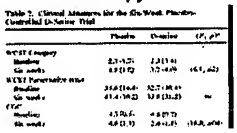
Negative



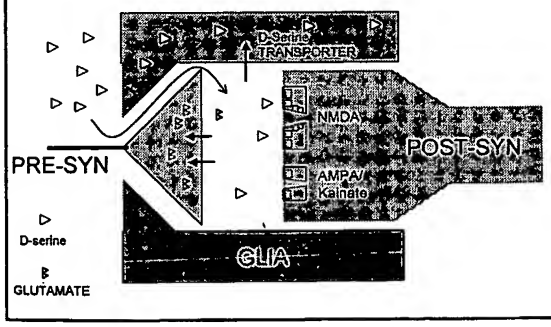
Cognitive



Neuropych



Glycine transporters as therapeutic targets



Analogy

Administering Glycine, D-serine is analogous to turning on faucet

Administering D-serine transport inhibitors is analogous to blocking the drain

Application demonstrates:

- Novel, D-serine transport system
- Novel compounds that block the novel system
  - D-serine dodecylamide
  - D-alanine dodecylamie
- Animal behavioral effects related to blockade
- Changes in in vivo NMDA binding related to novel compounds

US Appl 10/066,657

Issue 1: Were compositions known prior to submission?

Answer: No

Glycyldodecylamide was previously known

D-serine dodecylamide, D-alanine dodecylamide are novel compounds not previously known

Issue 2: What is undue experimentation?

Answer 1: Development of new drug for clinical treatment costs over $100M and takes over 5 yrs. Development of listed derivatives cost <$100K and took <6 mo. Objective criteria for undue experimentation need to be specified.

Issue 2: What is undue experimentation?

Answer 2: Only 2 compounds are needed to claim the genus. In case of this application, glycyldodecylamide, D-serine dodecylamide and D-alanine dodecylamide establish the genus

Control number 09/956,034

Issue 1: Do D-serine and D-serine transport inhibitors have a "common" mechanism of action?

Answer: No

1. D-serine does not inhibit D-serine transport

Proof: In example 1, D-[3H]serine is shown to be transported

2. GDA, DSerDA & DAlaDA do not bind to NMDA receptor

Proof: example 2, the NMDA glycine-site antagonist HA-966 was used to exclude the possibility that the prototype d-serine transport inhibitors described in the present application worked by binding to the NMDA glycine site (US2002/018 3390 A1, p. 2, last 4 lines - p. 3, 1st line)

Issue 2: Is D-serine the "active ingredient" of the compounds described in the specification?

Answer: No

None of the compounds described in the application contains the molecular entity D-serine. D-serine dodecylamide is a compound in which 12 carbons are added to a D-serine backbone. This is a different molecular entity. Two of the compounds, glycyldodecylamide and D-alanine dodecylamide, do not even have D-serine in their chemical composition.

Issue 3: "patient, condition to be treated and effect are all the same"

This is not a reasonable standard. This would imply that no new treatment for negative symptoms of schizophrenia could ever be patented since patient (schizophrenic), condition (negative symptoms) and effect (improvement) are all the same.

Molecular mechanism of action of D-serine and D-serine transport inhibitors are not the same

Issue 4: Compounds set forth in the appendix were not in the original application

Compounds demonstrate that one skilled in the art, using information set forth in the application could practice the invention without undue experimentation

Compounds synthesized for <$100K using commercial synthesis laboratory (Albany Molecular) in under 6 mo

Undue experimentation not required